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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/761,557	01/21/2004	D. James Surmeier	NWESTERN-08739	2838

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EXAMINER	
CHONG, KIMBERLY	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/761,557	SURMEIER ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group II, claims 4-10, in the reply filed on 07/25/2005 is acknowledged.

Status of the Application

Claims 4-10 are pending and currently under examination. Claims 1-3 and 11-16 have been cancelled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 4-10 broadly reads on any siRNA molecule that is directed against any mRNA encoding a Kv3.4 protein wherein the siRNA is capable of inhibiting Kv3.4 expression in any neuronal cell.

Although the specification states 21 siRNA sequences were synthesized and are targeted to a rat Kv3.4 gene (see page 67, line 4), the specification does not provide the sequences of the 21 siRNA and further does not provide information regarding what particular structure is directed against any mRNA encoding a Kv3.4 protein wherein the siRNA is capable of inhibiting Kv3.4 expression in any neuronal cell. The scope of the claimed invention is so broad that the skilled artisan would not be able to envisage the entire genus claimed of siRNA molecules that would inhibit any Kv3.4 RNA in any neuronal cells in any species. Not only do the claims read broadly on any Kv3.4 RNA, additionally the skilled artisan would not recognize that the applicant was in possession of the claimed invention at the time of filing. The ability for a specific siRNA to inhibit a particular gene must be determined experimentally and cannot be predicted.

Moreover, the general knowledge in the prior art concerning siRNA sequences does not provide any indication of what structure to what Kv3.4 gene will inhibit any Kv3.4 RNA in any neuronal cell in any species.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

MPEP 2163 states in part, "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical

properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")

Thus, the instantly claimed invention cannot be said to have been adequately described in a way that would convey with reasonable clarity to those skilled in the art that, as of the filling date sought, applicant was in possession of the claimed invention because the specification, while providing information on siRNA sequences targeted to Kv3.4 RNA, does not provide any other information or guidance as to what siRNA sequence for which Kv3.4 RNA will inhibit Kv3.4 expression in any neuronal cell in any species.

Claims 4-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for a method of inhibiting Kv3.4 expression in any neuronal cell in any subject *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant claims are broadly drawn to a method of inhibiting Kv3.4 expression in any fast-spiking neuronal cell using a siRNA targeted to any gene encoding Kv3.4 from any species. Further, the instant claims recite inhibiting the cell *in vivo, in vitro* or *ex vivo*.

The specification as filed discloses a method to decrease expression of Kv3.4 mRNA in murine globus pallidus or subthalamic neuronal cells after administration of a siRNA targeted to a gene encoding Kv3.4 *in vivo* (see Example 6), but this method is only prophetic. The specification further discloses *in vitro* administration of siRNA, targeted against a gene encoding Kv3.4, to HEK 293 cells, which are not neuronal cells, expressing Kv3.4 (see Example 6). The specification does not disclose a method of inhibiting Kv3.4 expression in any neuronal cell in any species *in vivo,* and further does not even disclose a method of inhibiting Kv3.4 expression in any neuronal cell in any species *in vitro or ex vivo*.

There is no guidance in the specification as filed that teaches how to target the claimed inhibitor directed against any gene encoding Kv3.4 in any neuronal cell in any species and further inhibit the expression of Kv3.4 in any neuronal cell in any species. Although the specification discloses decreased expression of Kv3.4 mRNA in non-neuronal HEK 293 cells *in vitro*, such a disclosure would not be considered enabling for inhibition of Kv3.4 in any neuronal cells in any species *in vivo* since the state of gene therapy using antisense or siRNA is highly unpredictable.

The following factors have been considered in the analysis of enablement: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the

inventor, (7) the existence of working examples, (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The claimed breadth of claims 4-10 encompass a method of inhibiting any Kv3.4 gene in any neuronal cell in any species by administering a siRNA targeted against a gene encoding Kv3.4. Although the specification discloses inhibition of the Kv3.4 expression in non-neuronal HEK 293 cells using siRNA (see Example 6), this guidance is not sufficient to resolve the known unpredictability in the art associated with appropriate *in vivo* delivery of an inhibitor to inhibit Kv3.4 expression in neuronal cells as provided by the instantly claimed methods.

The references cited herein illustrate the state of the art for therapeutic *in vivo* applications using antisense and RNAi. Green *et al.* states that "[i]t is clear from the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense [oligonucleotides] can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established. In addition, toxicity in humans appears more problematic than might be predicted based on preclinical studies in rodents. Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects" (Antisense Therapy in Human Disease; Vol. 191, No. 1 2000, pg 103 column 2). The problems with efficient delivery of antisense oligonucleotides to cells has been addressed by Jen *et al.*, who states that "[o]ne of the major limitations for the therapeutic use of AS-ODNS ...is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable (Stem Cells 2000; 18:307-319

pg 315 column 2)." Jen *et al.* concludes that "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive (see p 315, second column).

The state of the art for therapeutic *in vivo* applications for RNAi face similar hurdles as antisense as observed by Caplen (Expert Opin. Biol. Ther. 2003, 3(4): 575-586) who states "[m]any of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system, have been problems the gene therapy field has struggled with for over a decade now" (see page 581, last paragraph). Novina et al. (Nature 2004, Vol.430:161-164) agrees that the "major obstacle to therapeutic gene silencing is the 'delivery problem'- the necessity of introducing short dsRNAs into specific organs" (see page 164, third paragraph).

Paroo et al. (Trends in Biotechnology 2004, Vol.22(8):390-394) summarizes by stating "[d]eveloping siRNA for efficient gene silencing in vivo is likely to be more challenging and many issues must be addressed before use in animals can become routine. As with any compound, issues of adsorption, distribution, metabolism and excretion are significant obstacles. However, the duplex nature of siRNA introduced an additional layer of complexity. Even with the great progress that has been made, it is not clear whether or not siRNA possesses any advantages relative to traditional antisense oligonucleotides for in vivo experiments or therapeutic development. Crucial pharmacological and chemical challenges will need to be addressed before siRNA can fulfill its immense promise" (see page 393, last paragraph).

Although RNAi has been seen as the new magic bullet to silence genes, "...magic bullets need magic guns" (stated by William Pardridge as quoted by Adams in The Scientist (2005) Vol.19:Issue1). Adams notes that researchers have struggled to get their therapies to particular targets and as stated by McCaffrey "[t]heir approach involves injecting large amounts of virus [vectors expressing shRNA] into the tail vein of mice, or into an artery leading to the liver. Its efficient but probably isn't going to work for humans" (see page 2 The Scientist (2005) Vol.19:Issue1). Even some of the applicants of the instant application have noted the unpredictability of using siRNA injected into the vein and observes that "[i]n some cells, inhibition seemed nearly complete, whereas in others, low or moderate levels of EGFP were observed....These results may be due to incomplete inhibition in cells that take up lesser amounts of siRNA. High pressure delivery of fluorescently labeled siRNA reveals that in vivo uptake is not equal in all hepatocytes when this method is used' (Lewis et al. Nature Genetics 2002 Vol.32;107-108).

As outlined above, it is well known that there is a high level of unpredictability in the antisense and RNAi art for therapeutic *in vivo* applications. The scope of the claims in view of the specification as filed together do not reconcile the unpredictability in the art to enable one of skill in the art to make and/or use the claimed invention, namely inhibiting expression of a target endogenous gene *in vivo* by delivering polynucleotides to cells via injection into vessels. Delivery and inhibition of a luciferase marker gene in pig cells, as shown in the specification (Examples 1, 4 and 5) does not correlate with the ability to inhibit any endogenous gene expressed in mammalian heart cells

While one skilled in the art may be able to produce a siRNA targeted to a Kv3.4 gene in HEK 293 cells and inhibit Kv3.4 gene expression in HEK 293 cells, the specification as filed does not teach a method for inhibiting Kv3.4 in any neuronal cells in any species.

In view of the unpredictability in the art of antisense and RNAi-based therapy, as outlined above, the specification as filed does not provide adequate guidance that would show how one skilled in the art would practice the claimed invention without undue experimentation.

Given the teachings of the specification as discussed above, one skilled in the art would not know *a priori* whether introduction of any siRNA *in vivo* by the broadly disclosed methodologies of the instantly claimed invention, would result in successful inhibition of expression of a Kv3.4 gene in an neuronal cell.

To practice the claimed invention, one of skill in the art would have to *de novo* determine; the stability of the siRNA *in vivo*, delivery of the siRNA, specificity to the target tissue *in vivo*, dosage and toxicity *in vivo*, and entry of the siRNA into the cell *in vivo* and the effective action therein. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Please note that on July 15 2005, the Central FAX Number was changed to 571-273-8300. Faxes sent to the old number (703-872-9306) will be routed to the new number until September 15, 2005.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also

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Kimberly Chong
Examiner
Art Unit 1635